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The Risk of Bacteremia in Previously Healthy Children Presenting with Severe Neutropenia and Fever

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Abstract

Previously healthy children who present with fever and newly-discovered isolated neutropenia are often hospitalized and treated with broad-spectrum antibiotics until final cultures are obtained. While the risk of severe infections has been well studied in febrile patients presenting chemotherapy-induced neutropenia and those with severe congenital neutropenia, the risk of severe bacterial infection in previously healthy children has been poorly evaluated. Through a 6-year retrospective cohort study in a large tertiary-care pediatric center, we reviewed the outcomes of patients with isolated neutropenia and fever. We included children with severe neutropenia, defined as an Absolute Neutrophil Count (ANC) ≤ 0.5 × 10/L. All patients with prior history of neoplasia, chemotherapy, recurrent or chronic neutropenia and all patients under 3 months of age were excluded. Forty-seven children, median age of 1.1 years, were included. Median ANC was 0.2 × 10/L. Median hospital stay was 3 days. A seasonal incidence of febrile neutropenia emerged, likely correlating with viral epidemics. Forty-two patients (89.4%) received a diagnosis of probable viral infection, three (6.4%) had a urinary infection, one (2.1%) had pneumonia, and one (2.1%) had tonsillar abscess. Outcome was favorable for all patients. Blood cultures were negative for all patients.

Severe neutropenia with fever should not be an absolute indication for antibiotics and hospitalization in previously healthy children with reassuring physical examination. Physicians should guide their management based upon on usual diagnostic evaluation tools including thorough history, physical exam, imaging and other laboratory investigations.

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Introduction

Febrile Neutropenia (FN) has been extensively studied in the cancer setting, where the risk of sepsis and severe invasive bacterial infection is up to 20 and 29% respectively[1,2]. Children with severe congenital neutropenia are also at high risk of serious bacterial complications [3]. Considering the risk of significant morbidity and mortality, the management of such patients who present with fever and severe neutropenia, defined by an Absolute Neutrophil Count (ANC) ≤ 0.5 × 10^9/L, is well established. While healthy children with no significant prior medical history may present transient severe neutropenia, particularly during benign viral infections, few studies have assessed the risk of bacterial complications in such children presenting with FN. Consequently, children with no known medical conditions and with apparent viral neutropenia are often hospitalized and treated with broad-spectrum antibiotics. The aim of this study was to describe the outcomes of previously healthy children who presented to the Emergency Department (ED) with fever and isolated, severe, newly-discovered neutropenia.

Materials and Methods

Study design

This was a retrospective cohort study conducted at CHU Sainte-Justine, in Montreal, Canada, a large tertiary pediatric hospital that receives approximately 70,000 visits to its ED every year. Patient characteristics and clinical data were abstracted from hospital charts by a single reviewer. The CHU Sainte-Justine institutional ethics board approved the study.

Setting and population

Patients with neutropenia were identified through the CHU Sainte-Justine computerized ED database. All patients under the age of 18 years who presented with a history of fever (defined as a temperature ≥ 38.5° C) and severe neutropenia (defined as ANC ≤ 0.5 × 10^9/L) during a six-year period were included in this study. Only patients with severe neutropenia were targeted based

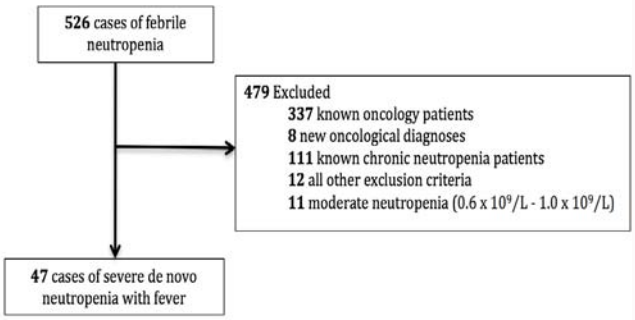

Figure 1: Flow diagram of study population.

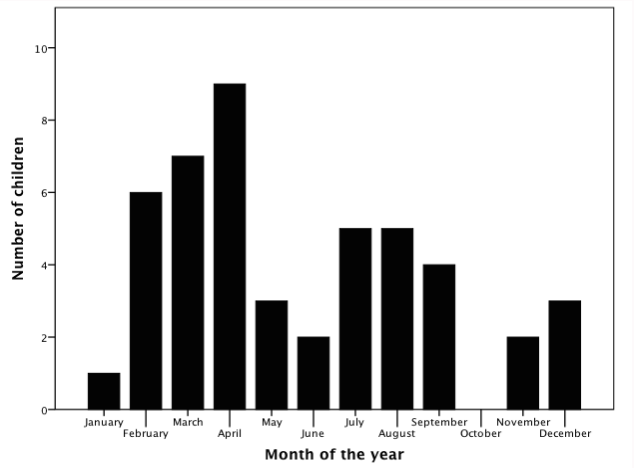

Figure 2: Monthly distribution of severe neutropenia with fever in previously healthy children.

upon the known risk of Serious Bacterial Infection (SBI), particularly bacteremia, in severely neutropenic cancer patients. Patients were excluded from this study if they presented known risk factors for SBI, independent of neutropenia. Consequently, all patients with a history of cancer, chemotherapy, bone marrow transplant, immunodeficiency, known neutropenia (either chronic or recurrent) and all patients under the age of 3 months were excluded from this study. All patients with non-isolated neutropenia on initial CBC were also excluded from this study.

Classification of results

A positive blood or CSF culture was defined as the isolation of a single pathogen. Positive urine specimen was defined as bacterial growth greater than 50×10^6 CFU/L of a single pathogen on a bladder catheter specimen, greater than 100×10^6 CFU/L of a single pathogen on a midstream urine sample, any growth from supra pubic aspiration or any growth of pseudomonas species. Pneumonia was defined as the presence of pulmonary opacity on chest x-ray as interpreted on final radiology reporting.

Data analysis

Results were analyzed with Microsoft Excel 2011 (Version 14.1.) and IBM SPSS 20.

Results

Over 6 years, 526 FN ED visits were recorded, of which 47 met the inclusion criteria (Figure 1). The median age was 1.1 years (range: 3 months to 6.1 years); 53.3% were male. The ethnic origin of the patients could not be studied since ethnicity was only sporadically reported in patient charts. Upon initial assessment by ED physicians, 91.5% of the children were described as "well-appearing". The median ANC was 0.2×10^9/L (range: 0×10^9/L to 0.5×10^9/L). There was a clear bimodal seasonal incidence, with 47% of cases occurring between February and April and 30% occurring between July and September (Figure 2). All but two patients (95.7%) were hospitalized with a median hospital stay of 3 days (Inter-quartile range: 2 to 4 days). Forty-three of the 47 patients (91.5%) were given intravenous broad-spectrum antibiotics using either a third-generation cephalosporin or a combination of either timentin with tobramycin or ampicillin with gentamicin, for a median duration of 2 ± 2.6 SD days. Blood cultures were performed in all patients and all were negative. Bacterial infection was suspected in five patients upon admission. Viral assays were only performed in a small number of patients (Table 1). One patient, aged 4.5 months, with decreased feeds, diarrhea and oral ulcers, was admitted in compensated shock requiring fluid resuscitation. Initial ANC was 0.0×10^9/L. He received ticarcilline-clavulanate and tobramycin. Three blood cultures, cerebrospinal fluid culture, urine culture and viral detection assays were negative. An external ear culture grew *pseudomonas aeruginosa*. Upon assessment by the ear-nose and throat specialist, this patient was found to have external otitis without underlying acute otitis media and topical treatment was initiated. All diagnostic imaging studies, including chest x-rays and cerebral CT scans were normal. Bone marrow assessment revealed no anomalies. The patient completely recovered and was eventually thought to have presented a viral shock. All patients included in this study had a favorable outcome. Final diagnoses are shown in Table 1.

Table 1: Discharge diagnoses and identified infectious etiologies.

Final diagnosis upon discharge	N (%)	Infectious agents identified	N (%)
Viral infection	42 (89.4)	Respiratory Syncytial Virus	1 (2.1)
		HHV6	1 (2.1)
		Rotavirus	1 (2.1)
Urinary tract infection	3 (6.4)	*E. coli*	2 (4.3)
		K. pneumonia	1 (2.1)
Pneumonia	1 (2.1)	-	-
Tonsillitis with suspected tonsillar abscess	1 (2.1)	-	-

Discussion

While up to 70,000 patients are seen yearly in our ED, only 47 cases of severe *de novo* neutropenia in previously healthy children were identified over a period of six years. In contrast to patients with severe chronic, congenital, or chemotherapy-induced neutropenic fever, we found that such cases are not associated with a high risk of severe bacterial infection. A review of published articles identified 433 pediatric cases of newly diagnosed severe neutropenia with fever in fourteen heterogeneous studies [4-17].

Our study adds 47 such cases to the literature. Some of these studies reveal that patients with fever and *de novo* severe neutropenia may present with bacteremia. However, they largely report sepsis with encapsulated bacteria with *haemophilus influenza* type B and *streptococcus pneumoniae* being the most frequent causal agents prior to the development and systematic use of conjugate vaccines [5,8]. Studies performed after the introduction of such vaccines demonstrate that the risk of bacteremia is extremely rare, and that bacteremia is typically not observed in febrile children who are clinically well-

appearing and who show no clinical evidence of bacterial infection. As in most pediatric conditions, clinical assessment is extremely important when it comes to patients presenting with febrile neutropenia. In a study performed in the preconjugate vaccine era, Bonadio showed that all patients with neutropenia and underlying severe bacterial infection had evidence of a fulminant disease process upon initial clinical examination. By contrast all 51 patients in this study who appeared well had negative cultures [8]. Similarly, in a study of febrile children with moderate to severe neutropenia, Melendez found only one septic child above the age of 3 months out of 1,888 previously-well children presenting with FN. This child also had a septic appearance upon initial presentation [9]. An association between viral infections and transient neutropenia has indeed been clearly demonstrated by past studies. Among potential causative agents, viral infection with HHV-6, Enteroviruses, Influenza, Parvovirus, EBV, Adenovirus and RSV have been well documented [5,7]. Unfortunately, our study failed to confirm such associations as viral detection assays were not routinely performed. However, while only three viral infections were ultimately confirmed (RSV, HHV6, Rotavirus), most patients had a clinical course suggestive of viral infection and eight had a clinical course highly suggestive of roseola (exanthem subitum). The finding of a seasonal variation in the incidence of severe *de novo* neutropenia with fever in our population further tends to support a viral etiology. Our study demonstrated peak-incidence between the months of February to April and July to September, correlating with usual epidemics of influenza, RSV and adenovirus, as well as enterovirus respectively, while HHV-6 may be observed throughout the year. This finding is consistent with that of Husain, who suggested a correlation between viral epidemics and possible higher occurrence of transient severe neutropenias [5]. Although prospective studies are still lacking, our study and the literature review further suggest that febrile children with *de novo* severe neutropenia are unlikely to present severe bacteremia if they are well-appearing. They may therefore not require broad-spectrum antibiotic administration or hospitalization. We suggest that such patients can safely be followed as outpatients. In our center, since this study, febrile children with *de-novo* severe isolated neutropenia are only hospitalized in case of abnormal clinical findings. All well-appearing children may receive one dose of intravenous ceftriaxone at the discretion of the ED physician with subsequent follow-up in our pediatric outpatient clinic.

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